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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/992,643
Filing Date: November 14, 2001
Appellant(s): BOTSTEIN ET AL.

Ginger R. Dreger
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 13 February 2006 appealing from the Office action mailed 15 August 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

09/989,328 (allowed)

09/990,436 (under appeal)

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Pennica et al., 1998, PNAS USA 95:14717-14722.

Konopka et al., Proc. Natl. Acad. Sci. (1986) 83:4049-4052.

Chen et al., 2002, Molecular and Cellular Proteomics 1:304-313.

Hu et al., 2003, Journal of Proteome Research 2:405-412.

LaBaer, 2003, Nature Biotechnology 21:976-977.

Haynes et al., 1998, Electrophoresis 19:1862-1871.

Gygi et al., 1999, Mol. Cell. Biol. 19:1720-1730.

Lian et al., 2001, Blood 98:513-524.

Fessler et al., 2002, J. Biol. Chem. 277:31291-31302.

Hanna et al., 1999, Pathology Associates Medical Laboratories.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The claims are directed to isolated polypeptides comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 207 with or without its signal peptide, or the amino acid sequence of the full-length coding sequence of the cDNA deposited under ATCC accession number 209951, wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors. It is noted that the phrase "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" is not an activity limitation for the claimed polypeptides; rather, it is a characteristic of a nucleic acid. In other words, the claims do not require that the claimed polypeptides be overexpressed in any tumor, or have any biological activity.

Claims are also presented to chimeric proteins comprising the aforementioned polypeptides. The specification discloses the polypeptide of SEQ ID NO: 207, also known as PRO1112. Appellants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Appeal Brief, p. 4, beginning of arguments. (It is noted that the specification asserts several other utilities for the claimed polypeptides, all of which have been found to be non-specific and/or insubstantial. For discussion of these utilities, see Office Action mailed 25 February 2004. However, these asserted utilities will not be re-addressed here due to Appellants' indication that they are relying upon the gene amplification assay for utility and enablement.)

At pages 539-555, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO1112 had a ΔCt value of at least 1.0 for six out of fourteen lung tumor samples and twelve out of fourteen colon tumor samples. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548, it is stated that samples are used if their values are within 1 Ct of the

'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

While these data support utility and enablement of PRO1112 *genomic DNA* for use in lung or colon tumor diagnosis, the data have no bearing on the utility of the claimed PRO1112 *polypeptides and polypeptide variants*. In order for PRO1112 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels, which in turn would have to correlate with increased polypeptide levels. No data regarding PRO1112 mRNA or PRO1112 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between mRNA levels and polypeptide levels. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not

related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

Moreover, even if increased mRNA levels could be established for PRO1112, it does not follow that PRO1112 polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean mRNA expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying mRNA changes of 5-fold or less in tumors compared to normal, there was no evidence of a correlation between altered mRNA expression and a known role in the disease. However, among genes with a 10-fold or more change in mRNA expression level, there was a strong and significant correlation between mRNA expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be

important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that transcript levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient"

(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who

found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

Therefore, data pertaining to PRO1112 genomic DNA do not indicate anything significant regarding the claimed PRO1112 polypeptides. The data do not support the specification's assertion that PRO1112 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO1112 polypeptides or variants thereof are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1112 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1112 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claims 119-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a

credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. This lack of enablement rejection applies to the PRO1112 polypeptide of SEQ ID NO: 207 as well as the claimed variants thereof.

Claims 119-123, 130 and 131 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with SEQ ID NO: 207, wherein said polypeptides are encoded by nucleic acids that are amplified in lung or colon tumors. It is noted that the phrase "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" is not an activity limitation for the claimed polypeptides; rather, it is a characteristic of a nucleic acid. In other words, the claims do not require that the claimed polypeptides be overexpressed in any tumor, or have any biological activity. Thus, the claims do not require that the *polypeptide* possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. The claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to

be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved, or any activity limitations. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 207, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

(10) Response to Argument

In general, Appellants' organization of arguments will be followed.

Appellants' Summary of Arguments

Issue 1: Utility/Enablement

At the middle of p. 4 of the Brief, Appellants argue that the patentable utility of PRO1112 polypeptides is based on the gene amplification data for the gene encoding the PRO1112 polypeptide. Appellants state that the specification shows significant amplification of the gene encoding PRO1112 in several different lung and colon tumors. Appellants refer to the declaration of Dr. Goddard (submitted under 37 C.F.R. § 1.132 on 04 August 2005) as explaining that a gene that is amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful for the diagnosis of cancer, for monitoring cancer development, and/or for

measuring the efficacy of cancer therapy. Appellants urge that such a gene is useful as a marker for the diagnosis of lung or colon cancer. This has been fully considered but is not found to be persuasive, as it does not address the utility of the claimed subject matter, i.e., PRO1112 *polypeptides* and their variants. It is maintained that the gene amplification assay does not provide a patentable utility for polypeptides because amplified genomic DNA is not predictive of increased mRNA or polypeptide levels, for reasons discussed herein. For example, the art indicates that gene amplification data do not correlate with increased mRNA levels or increased polypeptide levels (see Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al.). Since the instant claims are directed to polypeptides, this is a major concern. The Goddard declaration was not found to be sufficient to overcome the rejection; however, the Goddard declaration will be addressed at length later in this answer.

At the bottom of p. 4 to the middle of p. 5 of the Brief, Appellants argue that ample evidence has been provided to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded polypeptide is also expressed at an elevated level. Appellants refer to Orntoft et al., Hyman et al. and Pollack et al. as teaching that, in general, gene amplification increases mRNA expression. Appellants point to the Polakis declaration (submitted under 37 C.F.R. § 1.132 on 18 June 2004) as establishing that there is a general correlation between mRNA levels and polypeptide levels. Appellants urge that even if there were no correlation between gene amplification and mRNA/protein expression, a polypeptide encoded by a gene that is

amplified in cancer still has a patentable utility in that such yields in more accurate tumor classification, relying upon the declaration by Dr. Ashkenzi (submitted under 37 C.F.R. § 1.132 on 18 June 2004) and the Hanna et al. reference. Appellants note that the sale of gene expression chips to measure mRNA levels is a highly successful business. Appellants assert that the research community believes that the information obtained from these chips is useful. Finally, Appellants conclude that there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO1112 conveys utility to the claimed PRO1112 polypeptides. This has been fully considered but is not found to be persuasive. Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., and LaBaer all speak to large sets of genes and constitute evidence that polypeptide levels cannot be predicted from mRNA levels in general. The Polakis declaration will be addressed in detail later in this answer. Regarding the Ashkenazi declaration and the Hanna et al. reference, the specification does not disclose that the PRO1112 polypeptide levels increase **or** stay the same. Further research would be needed to determine PRO1112 polypeptide levels in cancers showing gene amplification of PRO1112 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PRO1112 polypeptides as claimed in this application are simply starting points for further research and investigation into potential practical uses of the polypeptides. The Ashkenazi declaration (submitted under 37 C.F.R. § 1.132 on 24 October 2003) will be addressed in detail later in this answer. The Hanna et al. reference actually supports the rejection, since Hanna et al.

show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding gene chips, it is submitted that evidence of financial success is not relevant to utility or enablement. Also, the chips may provide useful information about genes, but not polypeptides. Finally, products that provide only potential or preliminary results may also sell well in the research community since the researcher who buys them may plan to follow up any preliminary results obtained from the chips with experiments directed at measuring polypeptide levels.

From p. 5 to p. 6 of the Brief, Appellants take issue with the Hittelman et al., Haynes et al., Chen et al., Hu et al., Lian et al., and Fessler et al. references relied upon in the rejection, stating that the references do not show a lack of correlation between mRNA and protein expression in general. Appellants urge that, while there may be exceptions, the central dogma of molecular biology is that there is a general correlation between DNA, mRNA, and protein levels. Appellants again refer to Orntoft et al., Hyman et al., Pollack et al., and the Polakis declaration. Appellants urge that the art accepted use of array chips for detecting diagnostic markers lends further support that, in general, the skilled artisan would reasonably expect that the gene amplification data for the PRO1112 gene indicates that the PRO1112 polypeptide is overexpressed in lung and colon cancer and useful for the diagnosis of such. This has been fully considered

but is not found to be persuasive. It is maintained that the Haynes et al., Chen et al., Hu et al., Lian et al., and Fessler et al. references support the rejection by establishing that it is not more likely than not that mRNA levels are predictive of protein levels. Orntoft et al., Hyman et al., Pollack et al., and Polakis declaration do not tip the balance of evidence in favor of Appellants' position, and are not commensurate in scope with the claims which encompass PRO1112 variants. The merits of these pieces of evidence will be addressed below. Finally, the chips may provide useful information about genes, but not polypeptides. The skilled artisan recognizes this, and uses the chips to provide preliminary insight into which molecules may prove themselves useful as diagnostics upon further testing.

Appellants conclude that when the proper legal standard is applied, one reaches he conclusion that the present application discloses at least one patentable utility for the claimed PRO1112 polypeptides. Appellants urge that the specification provides detailed guidance as to how to identify and make polypeptides having at least 80-99% amino acid sequence identity to PRO1112. Appellants argue that the skilled artisan would understand how to make and use the recited polypeptide variants for the diagnosis of lung or colon cancer without undue experimentation. This has been fully considered but is not found to be persuasive, since the PRO1112 polypeptides and variants have no utility for the reasons set forth in the rejection under 35 U.S.C. § 101, above, they also are not enabled.

Issue 2: Written Description

At p. 7 of the Brief, Appellants argue that the claims recite structural features, 80-99% sequence identity to the native sequence of SEQ ID NO: 207, which are common to the genus. Appellants also argue that the claims recite a functional activity for the encoding nucleic acids, namely, that the encoding nucleic acid is amplified in lung or colon tumors. Appellants argue that the specification teaches how to make and test for such. Appellants conclude that a description of the claimed genus has been achieved by recitation of structural and functional characteristics. This has been fully considered but is not found to be persuasive. While a general structural recitation is present (at least 80% identical over the length of the protein), no specific structures are required (e.g., motifs, conserved areas, etc.). The specification provides no guidance regarding which structures are critical. Essentially, the specification invites the skilled artisan to make and test, which is not the legal standard. Most importantly, there is **no** functional recitation in the claims for the claimed polypeptides. The phrase "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" reflects a feature or characteristic of the encoding DNA, *but does not set forth any activity or feature of the claimed polypeptides.* The specification describes a single structure, PRO1112, which is not shown to have any useful feature or activity. Such does not constitute a representative number of species to support description of the claimed genus.

Appellants' Response to Rejections

ISSUE 1: Appellants argue that claims 119-126 and 129-131 are supported by a credible, specific, and substantial asserted utility, and thus, allegedly meet the utility requirement of 35 U.S.C. §§ 101/112, first paragraph

A. The legal standard for utility under 35 U.S.C. § 101

At pp. 8-11 of the Brief, Appellants review the legal standard for utility, with which the examiner takes no issue.

B. Proper application of the legal standard

At p. 11 of the Brief, Appellants argue that the evidentiary standard to be used is the preponderance of the totality of the evidence. Appellants urge that the examiner must establish that it is more likely than not that the skilled artisan would doubt the truth of the statement of utility. Appellants argue that the data in Example 170 (starting at p. 539 of the specification) describes results of a gene amplification assay. Appellants characterize the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Appellants assert that gene amplification is an essential mechanism for oncogene activation. Appellants review how the assay was performed, and reports that the gene encoding PRO1112 was significantly amplified in several lung and colon tumors. This has been fully considered but is not found to be persuasive. The data pertaining to gene amplification do not convey utility to the claimed polypeptides and variants thereof, since amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al.).

At p. 12 of the Brief, Appellants refer to the declaration of Dr. Goddard, submitted under 37 C.F.R. § 1.132 on 04 August 2005. Appellants quote from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Appellants conclude that one skilled in the art would consider the 2.092 to 4.807-fold amplification of the gene encoding PRO1112 in lung and colon tumors is significant and credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not the amplification of the gene encoding PRO1112 in lung and colon tumors is significant and credible. Credibility has never been questioned. However, the significance can be questioned relative to the *claimed* subject matter, namely, PRO1112 *polypeptides* ***and*** *variants thereof.* Hu et al. and Chen et al. speak to the strength of the opposing evidence, as do Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., and Fessler et al., discussed in the rejection above. The expert has interest in the outcome of the case since Dr. Goddard is listed as an inventor and is employed by the

assignee. Finally, the expert refers to three publications as factual support for the conclusions in the declaration. However, neither Livak et al. nor Heid et al. appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. Pennica et al. was found to support the rejection, as discussed in the rejection above. The Goddard declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1112 gene has *not* been associated with tumor *formation* or the *development* of cancer, nor has it been shown to be predictive of such. Similarly, the PRO1112 gene has *not* been shown to be useful to track the *efficacy of cancer therapy*. The specification merely demonstrates that the PRO1112 genomic DNA is amplified in some lung and colon cancers compared to normal DNA from blood. No mutation or translocation of PRO1112 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1112 mRNA or polypeptide *or variants thereof,* as claimed, are elevated in any cancerous tissue. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1112 is amplified in a variety of samples and invites the artisan to determine the significance of this increase relative to the claimed subject matter. It remains that, as evidenced by the references of record, the issue is simply not predictable, and the specification presents a mere invitation to experiment. Based on consideration of the preponderance of the totality of the evidence as a whole, the rejection is proper.

At p. 13 of the Brief, Appellants refer to Orntoft et al., Hyman et al., Pollack et al., and the Polakis and Ashkenazi declarations as evidence supporting the assertion that

gene amplification more likely than not correlates with increased polypeptide levels. Appellants urge that a correlation that meets a "necessary" or "always" standard is not appropriate. This has been fully considered but is not found to be persuasive. The instant rejection is not based upon a "necessary" or "always" standard. Rather, the preponderance of the totality of the evidence indicates that the rejection is proper.

C. Appellants argue that a *prima facie* case of lack of utility has not been established

At p. 13, Appellants take issue with the Pennica et al. and Konopka et al. references relied upon by the examiner. Specifically, Appellants characterize Pennica et al. as being limited to WISP genes, and does not speak to the correlation of gene amplification and protein expression for genes in general. Appellants point out that there was such a correlation for WISP-1 as disclosed by Pennica et al. Appellants characterize Konopka et al. as being limited to the abl gene, and not speaking to genes in general. Appellants conclude that the examiner must show evidence that it is more likely than not that the correlation does not exist, and that a *prima facie* case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene amplification for genes in general because they show a lack of correlation between gene amplification and gene product overexpression. The instant case also concerns a single gene. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al. The evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et

al., Konopka et al.), (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in the majority of cases (Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al.), and (3) no evidence has been brought forth regarding levels of PRO1112 mRNA levels or PRO1112 polypeptide levels in cancerous tissue. Finally, Pennica et al. provide clear evidence that the claimed PRO1112 variants do not have utility and are not enabled, since there is evidence that closely related WISP genes show unpredictable gene amplification, mRNA, and polypeptide levels.

At p. 14 of the Brief, Appellants argue that Haynes et al. support Appellants' position when they state that there was a general trend between protein expression and transcript levels. This has been fully considered but is not found to be persuasive because Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (p. 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Clearly, Haynes et al. are saying that mRNA levels do not predict protein levels, in general.

From p. 14 to p. 16 of the Brief, Appellants criticize the Hu et al. reference. Specifically, Appellants criticize Hu et al. for being based upon a statistical analysis of information from published literature rather than from experimental data. Appellants characterize Hu et al. as being limited to estrogen-receptor-positive breast tumor only. Appellants criticize the types of statistical tests performed by Hu et al. Appellants

conclude that, based on the nature of the statistical analysis performed in Hu et al., and the fact that Hu et al. only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO1112 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1112 protein can be used as a cancer diagnostic. Furthermore, Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. Also, Chen et al. (2002, Molecular

and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas (the same type of cancer for which PRO1112 tested positive). Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO1112 mRNA or polypeptide is overexpressed in cancer, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding Appellants' criticism of Hu et al.'s statistical analysis, Appellant is holding Hu et al. to a higher standard than their own specification, which does not provide *any* statistical analysis such as reproducibility, standard error rates, etc. Regarding Appellants' criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

At p. 16 of the Brief, Appellants argue that the Lian et al. publication is limited to differentiating myeloid cells and does not teach anything regarding a lack of correlation between mRNA levels and protein levels in general. Appellants also find fault with Lian et al. for using a relatively insensitive assay. This has been fully considered but is not found to be persuasive. Lian et al. show a lack of correlation between mRNA levels and polypeptide levels in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels.") This is directly on point for the instant issue. Furthermore, Appellants again hold the reference to a higher standard than their own specification. Lian et al. used an art-accepted method to measure polypeptide levels whereas the instant specification and evidence of record do not report using any method to detect PRO1112 polypeptide levels.

At p. 17 of the Brief, Appellants take issue with the Fessler et al. publication, stating that Fessler et al. is limited to studying a few proteins/RNAs and using an insensitive assay. This has been fully considered but is not found to be persuasive because Fessler et al. found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract), which is directly on point regarding the instant issue. Furthermore, Appellants again hold the reference to a higher standard than their own specification. Fessler et al. used an art-accepted method to measure polypeptide levels whereas the instant specification and evidence of record do not report using any method to detect PRO1112 polypeptide levels.

At p. 17 of the Brief, Appellants argue that Fessler et al. and Chen et al. are deficient for using 2D gels, which do not detect low abundance proteins. This has been fully considered but is not found to be persuasive. While 2D gels might exclude low abundance proteins, their use is valid for detectable proteins. Chen et al. focused on those mRNA which encoded proteins that were detectable on 2D gel (p. 308, col. 2). The method was sensitive enough to determine that proteins having different isoforms also often had different protein/mRNA correlation coefficients (p. 309, paragraph bridging col. 1-2). It was concluded that absolute protein level did not influence the correlation with mRNA (p. 310, col. 1). Additionally, the correlation coefficient was not arbitrarily chosen, but was based on detailed statistical analysis that resulted in those values above the assigned correlation coefficient to be considered significant if the designated difference was above the threshold (see paragraph bridging pages 307-308). The results of Chen lead to the conclusion that post-translation modifications are likely to affect the correspondence (or lack thereof) of mRNA to protein levels (see Discussion). Further it was shown (p. 309, col. 2, 5th line) that, "In addition to differences in the relationship between mRNA levels and protein expression among separate isoforms, some genes with very comparable mRNA levels showed a 24-fold difference in their protein expression. Genes with comparable protein expression levels also showed up to a 28-fold variation in their mRNA levels." Chen showed that not only with mRNAs that encode a single protein but also with nucleic acids that encode multiple isoforms, only a minority of mRNAs showed a correlation in levels of expression with

their encoded proteins. 2D-PAGE is a common method of protein analysis, when the limitations are taken into account, as with Chen et al., the results are noteworthy.

At p. 18 of the Brief, Appellants argue that of the 66 genes with no isoforms, 40/66 had a positive correlation between mRNA and protein expression (Table 1). In Table II, which showed 30 genes with multiple isoforms, 22/30 showed a positive correlation between one isoform of each gene. No genes showed a negative isoform correlation. The argument has been fully considered, but is not persuasive. On page 309, first full sentence, Chen et al. state, "Among the 69 genes for which only a single protein spot was known (Table I), nine genes (9/69, 13%) were observed to show a statistically significant relationship between protein and mRNA abundance..." Table I considered significance at $p<0.05$. It is unclear what Appellants are using as the criteria for positive correlation to determine that 40/66 genes showed a correlation. If the correlation is not significant, one cannot support presumptions concerning it. As to Table II, if one isoform out of, for example, three shows a correlation, that finding supports the unpredictability of mRNA/protein correlation levels. Contrary to Appellants' assertion that no genes showed a negative isoform correlation, α-1-Antitrypsin and PDI were shown to have such a negative isoform correlation. Further, a number of other proteins with isoform had some positive but insignificant correlations. These findings are particularly relevant to the PRO1112 variants encompassed by the claims. Chen et al. is relied upon for teaching that assumptions cannot be made concerning mRNA/protein correlation with a reasonably certainty. The paper clearly answered the question posed: Does mRNA expression correlate with protein expression in lung tumor

samples? The answer was 'no' in a majority of cases. This result directly supports the Examiner's finding that the art does not sustain a reasonable expectation that for any particular mRNA expressed in tumor, the amount of protein and encoding mRNA will correlate.

Also at p. 18 of the Brief, Appellants refer to Beer et al. Since this paper has not been brought forth on the record in a timely fashion for individual analysis by the examiner, it has not been considered and is not found to constitute evidence against the rejection.

At pp. 18-19 of the Brief, Appellants argue that Hu et al., Lian et al., and Fessler et al. do not conclusively teach that, in general, protein levels cannot be accurately predicted from mRNA/gene amplification levels. Appellants argue that insensitive protein detection methods and methodology may have resulted in underrepresentation of certain protein species. Appellants urges that Haynes et al. and Chen et al. show a general positive correlation between increased gene amplification, mRNA and protein levels. Appellants conclude that a *prima facie* case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. In the instant case, the asserted utility that PRO1112 polypeptides and variants thereof are useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for a PRO1112 polypeptide or variant thereof to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of PRO1112 polypeptide or variant between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) gene amplification

does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in healthy or diseased tissue (Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al.), and (3) no evidence has been brought forth regarding the levels of PRO1112 polypeptides or variants thereof in cancerous tissues. In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not PRO1112 polypeptides can be used as a cancer diagnostic agent.

D. Appellants argue that the gene amplification data establish a credible, specific, and substantial patentable utility for the claimed PRO1112 polypeptide

At pp. 19-20 of the Brief, Appellants argue that Example 170 states that amplification is associates with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers, and diagnostic determination of those cancers. Appellants urge that ample evidence has been submitted to show that, in general, if a gene is amplified in cancer it is more likely than not that the encoded protein is overexpressed. Appellants point to Orntoft et al., Hyman et al., and Pollack et al. in support thereof. Specifically, Appellants characterize Orntoft et al. as studying transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Appellants characterize Hyman et al. as

comparing DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Appellants characterize Pollack et al. as profiling DNA copy number alteration across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that one average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold increase in mRNA levels. Appellants conclude that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1112 would be correlated with elevated levels of mRNA,

much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in colon cancer.

At p. 20 of the Brief, Appellants refer to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed 18 June 2004. Appellants characterize the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Appellants conclude that all of the submitted evidence supports Appellants' position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased

mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO1112 (i.e., data regarding amplification of PRO1112 genomic DNA), and does not disclose any information regarding PRO1112 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., and Fessler et al., all discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung or colon tumors? How highly amplified were the genes that correlated with increased polypeptide levels? Were any of the data relevant to *variants* of the PRO genes and polypeptides?

At p. 20 of the Brief, Appellants note that the sale of gene expression chips to measure mRNA levels is a highly successful business. Appellant concludes that the

research community believes that the information obtained from the chips is useful (i.e., that it is more likely than not that the results are informative of protein levels). This has been fully considered but is not found to be persuasive. Evidence of commercial success has no bearing on the issue of utility. The research community could just as easily be interested in the gene chips as a way of providing preliminary results, which would then be followed up with actual testing of protein levels.

At pp. 21-22, Appellants discuss the Hittelman et al. reference. Hittelman et al. is no longer being relied upon to support the instant rejection in view of the allowance of the PRO1112 nucleic acid claims in 09/989,328.

At p. 22 of the Brief, Appellants conclude that the examiner has disregarded the evidence provided in the referenced articles based on misinterpretations of their teachings. Appellants urge that the standard of "more likely than not" has been met by the disclosure, declarations, and references to establish that it is more likely than not that an amplified gene correlates with overexpressed protein. Appellants urge that the references used to support the rejection do not present a *prima facie* case of lack of utility. Appellants point to specific portions of the specification as supporting how to make and use the claimed polypeptide for lung or colon cancer diagnosis. Specifically, Appellants argue that the specification discloses the sequence of PRO1112, including sequences comprising epitope tags of Fc regions, step-by-step protocols for making an expressing PRO1112 in appropriate host cells, step-by-step protocols for production of antibodies that bind PRO1112, and the gene amplification assay. Appellants conclude that the skilled artisan would know how to make and use the claimed polypeptide for the

diagnosis of lung or colon cancer. Appellant argues that, based on the disclosure and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not undue. This has been fully considered but is not found to be persuasive. The examiner concedes that the specification teaches how to make PRO1112 polypeptide. However, the specification fails to provide a substantial asserted utility for the claimed PRO1112 polypeptide and variants thereof as recited in the claims, and thus the specification also fails to enable the claimed PRO1112 polypeptide and variants (specifically, the specification fails to teach the skilled artisan how to use the claimed PRO1112 polypeptides without undue experimentation). As discussed above, the PRO1112 genomic DNA of SEQ ID NO: 206 was found to be amplified in lung and colon cancer samples. However, the literature reports that gene amplification does not correlate with increased mRNA levels (see Pennica et al., Konopka et al.). The literature also reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al., Gygi et al., Lian et al., Fessler et al.) or cancerous tissue (see Hu et al., LaBaer, Chen et al., Hanna et al.). These references particularly report that variant genes/proteins do not have the same patterns of amplification and overexpression (see especially Pennica et al. regarding the WISP genes and Hanna et al. regarding the HER-2 genes). In view of the totality of the evidence, the skilled artisan would not reasonably assume that PRO1112 polypeptide or variants thereof are overexpressed in certain lung and colon tumors based on the disclosure regarding gene amplification for a single PRO1112 gene (SEQ ID NO: 206) without actually testing for PRO1112 polypeptide overexpression to

reasonably confirm the specification's assertion that PRO1112 is overexpressed in lung and colon tumors. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently available form. In view of such, the asserted utility for PRO1112 polypeptide as a cancer diagnostic agent is not substantial. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

ISSUE 2: Appellants argue that claims 119-123, 130, and 131 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph

A. The legal test for written description

At pp. 22-24, Appellants review the legal standard for adequate written description, with which the examiner takes no issue.

B. Appellants argue that the disclosure provides sufficient written description for the claimed invention

At p. 24 of the Brief, Appellants argue that the specification reports the reduction to practice of the native amino acid sequence of SEQ ID NO: 207. Appellants point to pages of the specification for support of "native" sequences, methods to determine percent identity, what changes can be made to a PRO sequence, and methods of making PRO sequences. This has been fully considered but is not found to be persuasive. The structure of SEQ ID NO: 207 has been provided, and has adequate written description. However, no other structures that are at least 80% identical to that of SEQ ID NO: 207 and which are encoded by a nucleic acid that is amplified in lung

and colon tumors have been disclosed. Description of a single species is not representative of the claimed genus. The specification provides a broad brush discussion of making variant polypeptides, including a discussion of "conservative" amino acid substitutions. However, such is merely an invitation to experiment to find those which may be encoded by a nucleic acid that is amplified in lung or colon tumors. There is no detailed guidance regarding which parts of the PRO1112 structure of SEQ ID NO: 207 are critical, for example. With the exception of SEQ ID NO: 207, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Appellants argue that the claims recite the function that the nucleic acid encoding the polypeptides is amplified in lung or colon tumors. Appellants point to Example 170 as providing guidance for determining whether or not a nucleic acid is amplified in lung or colon tumors. This has been fully considered but is not found to be persuasive. The examiner strongly disagrees with Appellants that "wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" is a functional recitation *for the claimed polypeptides*. The recitation confers no biological activity, function, feature, or

characteristic to the polypeptide itself. The encoding nucleic acid is a separate molecule.

Appellants refer to their arguments and evidence that gene amplification correlates with increased mRNA levels and increased protein levels. This has been fully considered but is not found to be persuasive for the reasons set forth above addressing these arguments and evidence.

Appellants argue that whether or not the polypeptide itself is overexpressed in tumors is irrelevant to the question of adequate written description. Appellants urge that the claims characterize the recited polypeptides as having the property that their encoding nucleic acids are amplified in lung or colon tumors. Appellants point to the specification as disclosing how to make and test for such. This has been fully considered but is not found to be persuasive. Again, whether or not an encoding nucleic acid is amplified in a tumor or not is *not* a property of the polypeptide. The nucleic acid and polypeptide are separate molecules. Also, "make and test" is not the legal standard for adequate written description. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

At p. 25, Appellants argue that the examiner has acknowledged that SEQ ID NO: 207 is adequately described. The examiner takes no issue with this statement.

At p. 25, Appellants argue that the court in *Fiers v. Revel* held that if a conception of a DAN requires a precise definition, such as by structure, formula, chemical name, or physical properties, the a description also requires that degree of specificity. Appellants urge that *Fiers* does not apply to the instant claims because they are directed to polypeptide and no to nucleic acids. Similarly, Appellants urge that *Fiddes* does not apply as it is directed to nucleic acids and not polypeptides. This has been fully considered but is not found to be persuasive because Appellants take too narrow a view on the findings in *Fiers* and *Fiddes.* Nucleic acids and polypeptides are both naturally occurring biological molecules, and thus require similar descriptions, as recognized by the court in *Fiers*. At p. 1604, *Fiers v. Revel* states, "We thus determined that, irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, **like conception of any chemical substance**, requires a definition of that substance other than by its functional utility." (emphasis added)

Appellants argue that in *Fiddes v. Baird*, the BPAI held that party Fiddes' claims to a human gene for bFGF were separately patentable over party Baird's claims to a sequence encoding "mammalian" bFGF. The BPAI held that the party Baird was not entitled to an earlier filing date for failing to describe specific naturally occurring mammalian gene sequences. Appellants distinguish their application from this fact pattern by stating that SEQ ID NO: 207 is described as is its encoding nucleic acid, SEQ ID NO: 206. Appellants urge that the skilled artisan could determine whether a variant PRO1112 sequence falls within the parameters of the claimed invention. This has been fully considered but is not found to be persuasive. The instant specification

does not describe *any* sequences of variant PRO1112 polypeptides that are encoded by nucleic acids amplified in lung or colon tumors. The prior art shows that very closely related polypeptides have different patterns of expression in cancer, as do their mRNAs, and their genomic DNAs may or may not be amplified. See Pennica et al. and Hanna et al.

At pp. 27-28 of the Brief, Appellants refer to *Enzo Biochem., Inc. v. Genprobe, Inc.* Appellants argue that the court in *Enzo* adopted the standard that the written description requirement can be met by showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, such as complete or partial structure, other physical and/or chemical properties, functional characteristics, a correlation between structure and function, or a combination thereof. Appellants urge that the instant claims meet the standard set by *Enzo* in that the sequences are defined structurally (at least 80% identical to SEQ ID NO: 207) and functionally (encoded by a nucleic acid that is amplified in lung or colon tumors). Appellants argue that the skilled artisan would have known that Appellants had knowledge and possessed claimed polypeptides commensurate in scope with the claimed genus. This has been fully considered but is not found to be persuasive. The examiner maintains that "wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" is *not* a functional limitation of the claimed polypeptides. The skilled artisan cannot look at a variant PRO1112 polypeptide and determine whether or not the encoding nucleic acid is amplified in lung or colon tumors. There is no assay *that can be done on the polypeptide itself* that can tell the skilled artisan whether or not a variant PRO1112

polypeptide is encoded by a nucleic acid that is amplified in lung or colon tumors. The skilled artisan must first isolate the encoding nucleic acid for their variant and then test it. The instant specification simply does not disclose any PRO1112 variant polypeptides, whether or not they are encoded by nucleic acids that are amplified in tumors. In view of all of this, the rejection is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Argument

Appellants have not requested an oral hearing as of the date of this Examiner's Answer. However, if Appellants request an oral hearing, the examiner wishes to have the opportunity to present oral arguments.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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